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EXAMINER
CHAKRABARTI, ARUN K

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/055,109	Applicant(s) Shi
	Examiner Arun Chakrabarti	Art Unit 1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the *mailing date of this communication.*
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *5/30/02 and 1/23/02* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-98* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-39 and 95-98* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *40-94* are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ *Certified copies of the priority documents have been received.*
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ *Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).*

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 3
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action*

DETAILED ACTION

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-39, and 95-98, drawn to method of making nucleic acids, classified in class 435, subclass 91.2.

II. Claims 40-60, drawn to method of nucleic acid hybridization, classified in class 435, subclass 6.

III. Claims 61-81, drawn to diagnosis of a disease, classified in class 424, subclass 9.1.

IV. Claims 82-93, drawn to determining physiological or developmental state of a cell, classified in class 436, subclass 69.1.

V. Claim 94, drawn to computer, classified in class 700, subclass 90.

2. The inventions are distinct, each from the other because of the following reasons:

Inventions of Groups I and II-V are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions of method of making nucleic acids of Group I is not disclosed as capable of use together with method of nucleic acid hybridization of Group II, diagnosis of a disease of Group III, determining physiological or developmental state of a cell of Group IV and computer of Group V and they have different modes of operation, different functions, or different effects.

3. Inventions of Groups II and III-IV are related as combination and subcombination. Inventions in this relationship are distinct if it can be shown that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability, and (2) that the subcombination has utility by itself or in other combinations (MPEP § 806.05(c)). In the instant case, the combination as claimed does not require the particulars of the subcombination as claimed because diagnosis of a disease can be carried out without hybridization of nucleic acid, e.g. by microscopic or immunoblot procedure. Similar logic is applicable to determining physiological or developmental state of a cell of Group IV . The subcombination of nucleic acid hybridization has separate utility such as PCR reaction or synthesizing double-stranded nucleic acid.

4. Inventions of Groups II and V are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the nucleic acid hybridization of Group II can be practiced with the computer of Group V or manually.

5. Inventions of Groups III and IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions of diagnosis of a disease of Group III is not disclosed as capable of use

together with determining physiological or developmental state of a cell of Group IV and they have different modes of operation, different functions, or different effects.

6. Inventions of Groups III and V are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the diagnosis of a disease of Group III can be practiced with the computer of Group V or by microscopic or immunoblot procedure.

7. Inventions of Groups IV and V are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case determining physiological or developmental state of a cell of Group IV can be practiced with the computer of Group V or manually by a microscope.

8. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

9. During a telephone conversation with James Butler on April 29, 2002 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-39 and 95-98. Affirmation of this election must be made by applicant in replying to this Office action. Claims

40-94 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

10. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1-4, 6-7, 9-18, 20, 21, 26-30, 34-36, and 95-97 are rejected under 35 U.S.C. 103(a) over Warthoe (PCT International Publication Number WO 98/51789) (November 11, 1998) in view of Marshall et al. (U.S. Patent 5,420,032) (May 30, 1995).

Warthoe teaches a method for constructing a nucleic acid library comprising:

a) obtaining a population of end-labeled double-stranded cDNA molecules (Figure 1 and Page 3, lines 9-23);

b) dividing the population into a first portion and a second portion (Page 15, line 28 to Page 16, line 2);

c) digesting the first portion with at least one sequence-specific endonuclease (Page 15, line 28 to Page 16, line 2);

d) digesting the second portion with another endonuclease (Page 15, line 28 to Page 16, line 2 and figure 2);

e) isolating nucleic acid fragments from the endonuclease digestion of the first and second portions using the end-labels (Figures 1-2 and Page 15, line 28 to Page 16, line 2);

f) digesting the fragments of the first portion with the at least one endonuclease of d) (Figure 2);

g) digesting the fragments of the second portion with the at least one endonuclease of c) (Figure 2);

h) removing labeled nucleic acid fragments from the first and second portions while retaining unlabeled fragments (Figures 2-3);

I) adding a population of adapters, the population containing adapters specific for the endonucleases used, wherein each adapter comprises a first region specific to a particular endonuclease used and a second region containing a primer binding site (Figure 1);

j) hybridizing and ligating the adapters to the unlabeled fragments (Figure 1);

k) amplifying the fragments using the adapters (Figure 1);

l) separating the amplified fragments by size (Figure 1).

Warthoe teaches a method, wherein the at least one sequence-specific endonuclease comprises at least 6 different sequence-specific endonucleases (Page 15, lines 12-27).

Warthoe teaches a method, wherein the at least one sequence-specific endonuclease is selected from at least one endonuclease having a 4 base recognition sequence (Page 15, lines 12-27).

Warthoe teaches a method, further comprising sequencing and quantifying the separated fragments of l) (Figure 1);

Warthoe teaches a method, wherein the primer binding region of the adapters does not have a significant homology to sequences known to be in the population of nucleic acid molecules (Page 16, lines 4-27);

Warthoe teaches a method, wherein the primer binding region of the adapters comprise no more than 2 and 10 different sequences ();

Warthoe teaches a method, wherein the end-labeled nucleic acid molecules are obtained by a method comprising, isolating poly mRNA from a cell, hybridizing a 5' end labeled an oligo dT

primer to the poly A mRNA, synthesizing a first cDNA strand by extension of the primer, and synthesizing a second cDNA strand by nick translation to produce double stranded cDNA (Figure 12)

Warthoe teaches a method, wherein the oligo dT primer has a sequence comprising L-(T)nVN, where L is a label at the 5' end of the primer and n is an integer between 4 and 50 ().

Warthoe teaches a method for constructing a nucleic acid library comprising: obtaining a population of 3' end-labeled double-stranded cDNA molecules by a method comprising, isolating poly mRNA from a cell; hybridizing a 5' end-labeled primer containing an oligo dT tail to the polyA mRNA; synthesizing a first cDNA strand by extension of the primer; and synthesizing a second cDNA strand by nick translation to produce a double stranded cDNA (Page 12, lines 15-31 and Figure 3 and Page 29, line 1 to page 30, line 11).

Warthoe teaches a method, wherein the adapters comprise a first region specific to a particular endonuclease and a second common primer binding site (Figure 1 and Page 16, line 4 to page 19, line 24).

Warthoe does not teach a method of digesting nucleic acid molecules with an endonuclease having a degenerate recognition sequence.

Marshall et al. teach a method of digesting nucleic acid molecules with an endonuclease having a degenerate recognition sequence (Abstract and Column 4, line 52 to Column 5, line 6).

Warthoe does not teach a method, wherein the at least one endonuclease having a degenerate recognition sequence produces fragments comprising unpaired overhangs containing

N to the power m unique sequences where N is the extent of degeneracy and is an integer between 2 and 4, and m is the number of bases in the unpaired overhang and is an integer between 2 and 6.

Marshall et al. teach a method wherein the at least one endonuclease having a degenerate recognition sequence produces fragments comprising unpaired overhangs containing N to the power m unique sequences where N is the extent of degeneracy and is an integer between 2 and 4, and m is the number of bases in the unpaired overhang and is an integer between 2 and 6 and wherein N to the power m equals at least 64 (Table 2 and Examples I and II) .

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute a method of digesting nucleic acid molecules with an endonuclease having a degenerate recognition sequence of Marshall et al. into the method of Warthoe, since Marshall et al. state, "The homing endonuclease of the present invention is novel and extremely useful because it cleaves double-stranded DNA at specific, infrequent sites, for which endonucleases were not previously available. The resulting fragments are of great value for human gene mapping because the cleavage sites are sequences ordinarily encountered in genomic DNA, and because cleavage by the endonuclease produces relatively larger fragments than characteristics of those produced by many previously available endonucleases (Column 4, line 65 to Column 5, line 6). " By employing scientific reasoning, an ordinary artisan would have combined and substituted a method of digesting nucleic acid molecules with an endonuclease having a degenerate recognition sequence of Marshall et al. into the method of Warthoe, in order

to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute a method of digesting nucleic acid molecules with an endonuclease having a degenerate recognition sequence of Marshall et al. into the method of Warthoe, in order to achieve the express advantages , as noted by Marshall et al., of a novel homing endonuclease that is extremely useful because it cleaves double-stranded DNA at specific, infrequent sites, for which endonucleases were not previously available and the resulting fragments are of great value for human gene mapping because the cleavage sites are sequences ordinarily encountered in genomic DNA, and because cleavage by the endonuclease produces relatively larger fragments than characteristics of those produced by many previously available endonucleases.

13. Claims 23-25 and 37-39 are rejected under 35 U.S.C. 103(a) over Warthoe (PCT International Publication Number WO 98/51789) (November 11, 1998) in view of Marshall et al. (U.S. Patent 5,420,032) (May 30, 1995) further in view of Oliner et al. (U.S. Patent 6,340,565 B1) (January 22, 2002).

Warthoe in view of Marshall et al teach the method of claims 1-4, 6-7, 9-18, 20, 21, 26-30, 34-36, and 95-97 as described above.

Warthoe in view of Marshall et al do not teach the method, wherein isolating and removing of end-labeled nucleic acid molecules is by particles that bind the end-labeled nucleic acid molecules and wherein the label and the particles are biotin and streptavidin respectively.

Oliner et al. teach the method, wherein isolating and removing of end-labeled nucleic acid molecules is by particles that bind the end-labeled nucleic acid molecules and wherein the label and the particles are biotin and streptavidin respectively (Column 16, lines 24-60).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute a method, wherein isolating and removing of end-labeled nucleic acid molecules is by particles that bind the end-labeled nucleic acid molecules and wherein the label and the particles are biotin and streptavidin respectively of Oliner et al. into the method of Warthoe in view of Marshall et al since Oliner et al. state, "Detectable labels suitable for use in the present invention include any composition detectable by spectroscopic, photochemical, biochemical, immunochemical, electrical, optical or chemical means. Useful labels in the present invention include biotin for staining with labeled streptavidin conjugate (Column 16, lines 45-51) ". By employing scientific reasoning, an ordinary artisan would have combined and substituted a method, wherein isolating and removing of end-labeled nucleic acid molecules is by particles that bind the end-labeled nucleic acid molecules and wherein the label and the particles are biotin and streptavidin respectively of Oliner et al. into the method of Warthoe in view of Marshall et al in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute a method, wherein isolating and removing of end-labeled nucleic acid molecules is by particles that bind the end-labeled nucleic acid molecules and wherein the label and the particles are biotin and streptavidin respectively of Oliner et al. into the method of Warthoe in view of Marshall et al , in order to

achieve the express advantages , as noted by Oliner et al., of useful labels that include biotin for staining with labeled streptavidin conjugate.

14. Claims 5, 19, and 31 are rejected under 35 U.S.C. 103(a) over Warthoe (PCT International Publication Number WO 98/51789) (November 11, 1998) in view of Marshall et al. (U.S. Patent 5,420,032) (May 30, 1995) further in view of Fox et al. (U.S. Patent 6,140,086) (October 31, 2001).

Warthoe in view of Marshall et al teach the method of claims 1-4, 6-7, 9-18, 20, 21, 26-30, 34-36, and 95-97 as described above.

Warthoe in view of Marshall et al do not teach the method, wherein the at least one sequence-specific endonuclease is selected from the group consisting of EcoRI, Hind III, Bam H1, Nco I, and Xho I.

Fox et al. teach the method, wherein the at least one sequence-specific endonuclease is selected from the group consisting of EcoRI, Hind III, Bam H1, Nco I, and Xho I (Column 17, lines 46-67).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the method, wherein the at least one sequence-specific endonuclease is selected from the group consisting of EcoRI, Hind III, Bam H1, Nco I, and Xho I. of Fox et al. into the method of Warthoe in view of Marshall et al since Fox et al. state, "Restriction endonucleases that may be advantageously used in the methods of the invention include, but are not limited to, EcoRI, Hind III, Bam H1, Nco I, and Xho I (Column 17, lines 57-

63)". By employing scientific reasoning, an ordinary artisan would have combined and substituted the method, wherein the at least one sequence-specific endonuclease is selected from the group consisting of EcoRI, Hind III, Bam H1, Nco I, and Xho I. of Fox et al. into the method of Warthoe in view of Marshall et al in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute the method, wherein the at least one sequence-specific endonuclease is selected from the group consisting of EcoRI, Hind III, Bam H1, Nco I, and Xho I. of Fox et al. into the method of Warthoe in view of Marshall et al, in order to achieve the express advantages , as noted by Fox et al., of restriction endonucleases that may be advantageously used to produce a collection of digested molecules.

15. Claims 8, 22, 32, and 98 are rejected under 35 U.S.C. 103(a) over Warthoe (PCT International Publication Number WO 98/51789) (November 11, 1998) in view of Marshall et al. (U.S. Patent 5,420,032) (May 30, 1995) further in view of Jones et al. (U.S. Patent 6,372,479 B1) (April 16, 2002).

Warthoe in view of Marshall et al teach the method of claims 1-4, 6-7, 9-18, 20, 21, 26-30, 34-36, and 95-97 as described above.

Warthoe in view of Marshall et al do not teach the method, wherein at least one endonuclease having a degenerate recognition sequence is Bsl I.

Jones et al. teach the method, wherein at least one endonuclease having a degenerate recognition sequence is Bsl I (Column 8, lines 13-49).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute a method, wherein at least one endonuclease having a degenerate recognition sequence is Bsl I of Jones et al. into the method of Warthoe in view of Marshall et al since Jones et al. state, "Without being limited thereto, preferred restriction sites include: DraIII, SfiI, PfiM1, MwoI, BslI, BglI, and AlwNI. Each of these enzymes generate 3' cohesive ends with overhangs having a length of 3 nucleotides (Column 8, lines 16-19) ". By employing scientific reasoning, an ordinary artisan would have combined and substituted a method, wherein at least one endonuclease having a degenerate recognition sequence is Bsl I of Jones et al. into the method of Warthoe in view of Marshall et al in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute a method, wherein at least one equivalent endonuclease having a degenerate recognition sequence is BslI of Jones et al. into the method of Warthoe in view of Marshall et al , in order to achieve the express advantages , as noted by Jones et al., of preferred restriction sites including BslI, which generates 3' cohesive ends with overhangs having a length of 3 nucleotides.

16. Claim 33 is rejected under 35 U.S.C. 103(a) over Warthoe (PCT International Publication Number WO 98/51789) (November 11, 1998) in view of Marshall et al. (U.S. Patent 5,420,032) (May 30, 1995) further in view of Fox et al. (U.S. Patent 6,140,086) (October 31, 2001) further in view of Jones et al. (U.S. Patent 6,372,479 B1) (April 16, 2002).

Warthoe in view of Marshall et al further in view of Fox et al. teach the method of claims 1--7, 9-21, 26-30, 31, 34-36, and 95-97 as described above.

Warthoe in view of Marshall et al further in view of Fox et al. do not teach the method, wherein at least one endonuclease having a degenerate recognition sequence is BslI.

Jones et al. teach the method, wherein at least one endonuclease having a degenerate recognition sequence is Bsl I (Column 8, lines 13-49).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute a method, wherein at least one endonuclease having a degenerate recognition sequence is Bsl I of Jones et al. into the method of Warthoe in view of Marshall et al further in view of Fox et al. since Jones et al. state, "Without being limited thereto, preferred restriction sites include: DraIII, SfiI, PfiM1, MwoI, BslI, BglI, and AlwNI. Each of these enzymes generate 3' cohesive ends with overhangs having a length of 3 nucleotides (Column 8, lines 16-19) ". By employing scientific reasoning, an ordinary artisan would have combined and substituted a method, wherein at least one endonuclease having a degenerate recognition sequence is BslI of Jones et al. into the method of Warthoe in view of Marshall et al further in view of Fox et al. in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute a method, wherein at least one equivalent endonuclease having a degenerate recognition sequence is BslI of Jones et al. into the method of Warthoe in view of Marshall et al further in view of Fox et al., in order to

achieve the express advantages , as noted by Jones et al., of preferred restriction sites including BslI, which generates 3' cohesive ends with overhangs having a length of 3 nucleotides.

Conclusion

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph. D., whose telephone number is (703) 306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119. The fax phone number for this Group is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237.

Arun Chakrabarti,

Patent Examiner,

March 18, 2003